INTRODUCTION AND OPENING REMARKS

Donald A. Middlebrook
Vice President, Regulatory Affairs and Quality Assurance
Thoratec Corporation
PRESENTATION OUTLINE

• Introduction and Opening Remarks
• Device Overview
• Clinical Results from REMATCH Trial
• Summary and Closing Remarks
# INTRODUCTION AND OPENING REMARKS

**Presenters:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Victor Poirier</td>
<td>Chief Technology Advisor</td>
<td>Thoratec Corporation</td>
</tr>
<tr>
<td>Dr. Eric Rose</td>
<td>REMATCH PI &amp; Chairman, Dept. of Surgery</td>
<td>Columbia-Presbyterian Medical Center, NY</td>
</tr>
<tr>
<td>Dr. Lynne Warner Stevenson</td>
<td>Medical Management Committee Chair, Director, Cardiomyopathy and Heart Failure</td>
<td>Brigham &amp; Woman’s Hospital, Boston</td>
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</tbody>
</table>
INTRODUCTION AND OPENING REMARKS

Thoratec Corporation Overview:

- Company Founded in 1976
- Merged with Thermo Cardiosystems in February 2001
- Product Focus
  - Circulatory Support
  - Vascular Grafts
  - Diagnostic Blood Testing
- Corporate Offices – Pleasanton, California
- 700 Employees Worldwide
- World Leader in Cardiac Assist Devices
INTRODUCTION AND OPENING REMARKS

Thoratec HeartMate VE LVAS; PMA P920014/ S16

- Contains Results from REMATCH* Trial
- Landmark RCT: HeartMate VE LVAS vs. Optimal Medical Management
- Cooperative Agreement between Thoratec, NIH/NHLBI and Columbia University
- PMA seeks FDA Approval to Expand Current HeartMate VE LVAS Indications For Use to Include:
  - Patients with end-stage left ventricular failure who are ineligible for cardiac transplantation

*Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart failure
DEVI CE OVERVI EW

Victor Poirier
Chief Technology Advisor
Thoratec Corporation
DEVICE OVERVIEW

- Heart
- Aorta
- External Battery Pack
- System Controller
- Air Vent with Vent Filter inserted
- HeartMate SNAP-VE LVAD
- Y-Connector
- Left side Battery omitted for clarity
VE vs SNAP Changes

VE

Suture

Locking screw rings

Bend relief

Suture not applied

SNAP
VE LVAD Reliability

Long term *in-vitro* testing:

- 88% chance that LVAD free of critical failures at 1 year
- 76% chance that LVAD free of critical failures at 2 years
- 3.1 year estimated mean time to failure

All based on 90% confidence intervals
HeartMate ® VE LVAS Continuous Improvement

VE
- Double lead
- Single lead left lower quadrant exit site

SNAP VE
- Outflow Bend Graft Relief
- Locking Screw Rings
- Improved System Controller Battery Module

VE
- Single lead right upper quadrant exit site

XVE
- eXtended, smaller diameter lead
- Low stress diaphragm
- Direct System Controller connection
Evolution of the HeartMate LVAS

Average duration / maximum duration of support

**REMATCH Trial (1998-2001)**
344 days* / 1130 days*

**PREMATCH Trial (1996-1998)**
276 days / 607 days

**HeartMate VE Bridge to Transplant Trial (1991-1998)**
113 days / 691 days

**HeartMate IP Bridge to Transplant Trial (1986-1994)**
69 days / 344 days

**Model 7/ 10 LVAD Trial (1975-1988)**
4 days / 41 days

*Ongoing patients
Conclusions

- VE LVAS is a clinically proven technology for bridge to transplant
- Worldwide VE LVAS experience provides strong platform for expanded indication
- Company dedicated to circulatory support and heart failure patients
- Commitment to continuous improvement
REMATCH TRIAL CLINICAL RESULTS

Eric Rose, MD
REMATCH Principal Investigator
Chairman, Department of Surgery
Columbia University
New York, NY
Summary of Critical Clinical Findings

**Efficacy:**
- Survival benefit is clear and clinically meaningful and QOL is equivalent to, if not better than, OMM.

**Safety:**
- Incidence of adverse events in context of mortality reduction and QOL trends provides reasonable assurance of safety.

**Conclusion:**
- The VE LVAS is a scientifically validated alternative therapy for end stage heart failure patients who are not candidates for cardiac transplantation.
Clinical Results from REMATCH Trial

Discussion Outline:

• History of the REMATCH Trial
• Trial Design and Administration
• Summary of Patient Population
• Effectiveness Results
• Safety Results
• Summary
History of the REMATCH Trial

- Need for treatment options in end stage heart failure patients
- Positive experience with VE LVAD
- Pilot Trial (1996 – 1998): 10 controls, 11 LVADs
  - Randomization shown to be feasible
  - Clinical equipoise supported, thus randomization remained ethical
- REMATCH Trial enrollment commenced May 1998
Design of REMATCH Trial

- Cooperative agreement between Thoratec, Columbia University and NIH/NHLBI
- Independent Coordinating Center (InCHOIR)*
- Multicenter, randomized controlled trial
- Patients & physicians not blinded to treatment assignment
- Prospective plan for interim analyses
- Intent to treat analysis
- Primary statistical analysis: Kaplan – Meier and Logrank

*International Center for Health Outcomes and Innovation Research
To Control Bias

- Randomization
- Independent Coordinating Center (InCHOIR)
- Thoratec blinded to control data
- Investigators, InCHOIR blinded to overall data
- Credentialed investigators: cardiologist and surgeon
- Gatekeeper: reviews each patient eligibility
- Independent Data Safety & Monitoring Board and Morbidity & Mortality committee
- Medical and Surgical Management committees
Key Study Objectives

- **Efficacy:** To evaluate the effect of VE LVAS on the survival of patients with end stage chronic heart failure who are ineligible for cardiac transplantation

- **Safety:** Document and analyze adverse events and the incidence of device malfunction and failure
Secondary Study Endpoints

- Quality of Life
- Functional status
- Days in and out of hospital
- Cardiovascular mortality
- Cost
Key Study Assumptions

- Patients and clinicians would not adopt LVAD unless all-cause mortality over 2 years reduced by 1/3 or more

- Safety performance of device documented through bridge to transplant experience

- QOL with LVAD should equal or exceed OMM group
Sample Size and Power

**Power:**
- Study powered for survival and not secondary objectives
- Survival over time is roughly exponential and that the hazard ratio (LVAS to OMM) is 0.56

**Sample Size/Endpoint:**
- Endpoint is number of deaths, not pts enrolled
- 92 deaths required to have 80% power in a logrank test
- Study designed to allow up to 140 pts
Randomization

- Patients randomized between LVAD and OMM arm in a 1:1 ratio
- Stratified by study center
- Blocked to maintain balance in center over time
- Block sizes randomly selected to prevent manipulation of treatment assignment
REMATCH Study Sites

- Columbia Presbyterian Med Ctr
- Cleveland Clinic Foundation
- Texas Heart Institute
- St Lukes Med Ctr, Milwaukee
- Temple University Hospital
- Rush Presbyterian Med Ctr
- Inova Fairfax Hospital
- LDS Hospital
- Ochsner Clinic
- Sharp Memorial Hospital
- Univ of Iowa Hospital & Clinic
- Univ of Michigan Hospital
- Univ of Minnesota Med School
- Brigham & Women’s Hospital
- Nebraska Heart Institute
- Loyola University Med Ctr
- West Penn Allegheny Health Systems
- Univ Washington Med Ctr
- Univ Alabama
- Univ of Texas Southwest Med Ctr
- Jewish Hospital, Louisville
REMATCH TRIAL CLINICAL RESULTS

Lynne Warner Stevenson, MD
Chair, Medical Management Committee
Director, Cardiomyopathy & Heart Failure Failure
Brigham & Women’s Hospital
Boston, MA
Heart Failure Populations

Preserved EF

Class III-IV

End-Stage 50-100K

Age 20-80 LowEF

> 80 Low EF

>80 EF>40

20-80 EF>40

> 80
REMATCH Eligibility Criteria

- NYHA Class IV symptoms for 60 out of 90 days on ACEI, digoxin, diuretics
- LVEF ≤ 25%
- Peak VO₂ ≤ 14 ml/kg/min or IV inotrope dependent
- Ineligible for cardiac transplantation
Reasons patients not transplant candidates

- Age $\geq$ 65 years
- Insulin dependent Diabetes Mellitus with end-organ damage
- Chronic renal failure
- Significant irreversible comorbidity
  - Cancer
  - Obesity
  - Pulmonary hypertension
Escalating Therapy for Heart Failure

Asymptomatic  Symptomatic  Severe  End-stage

- Cardiac replacement therapies
- Beta blockers
- Angiotensin Converting Enzyme Inhibitor
- Digoxin
- Diuretics for fluid retention
- Re-adjustment of Rx, more diuretics, + nitrates, hydral
- Spiro if normal K handling
- Investigational Rx

“Inotropic Rx
“Until”? 

HEART FAILURE MANAGEMENT PROGRAMS  HOSPICE
Renal Dysfunction in Heart Failure Trials

- SOLVD
- RALES
- ESCAPE
- REMATCH

Creatinine (mg/dl)

[Bar chart showing creatinine levels for different trials]
## REMATCH Therapies at Baseline

<table>
<thead>
<tr>
<th>Medication</th>
<th>% of OMM Patients (N = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td>53%</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>20%</td>
</tr>
<tr>
<td>IV Inotropes</td>
<td>75%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>97%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>85%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>46%</td>
</tr>
</tbody>
</table>
Patients not able to take ACEI

Most common reasons in Class IV:
- symptomatic hypotension
- and renal dysfunction
## Hospitalized Patient Populations After ACEI Rx

<table>
<thead>
<tr>
<th></th>
<th>CONS</th>
<th>VMAC</th>
<th>OPT</th>
<th>Profile B-Warm</th>
<th>FIRST^T</th>
<th>Profile C-cold</th>
<th>REMATCH OMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>119</td>
<td>121</td>
<td>120</td>
<td>114</td>
<td>107</td>
<td>103</td>
<td>103</td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td>26%</td>
<td>24%</td>
<td>26%</td>
<td>19%</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>Na</td>
<td>138</td>
<td>138</td>
<td>137</td>
<td>138</td>
<td>138</td>
<td>136</td>
<td>135</td>
</tr>
<tr>
<td>6 mo Mortality</td>
<td>29%</td>
<td>23%</td>
<td>10%</td>
<td>2 mo 20%</td>
<td>37%</td>
<td>34%</td>
<td>48%</td>
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</table>
Medical Management of OMM Population

<table>
<thead>
<tr>
<th>Medications</th>
<th>Baseline</th>
<th>Month 1</th>
<th>Last</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropes 1</td>
<td>75%</td>
<td>63%</td>
<td>70%</td>
</tr>
<tr>
<td>Inotropes ≥ 2</td>
<td>51</td>
<td>50</td>
<td>57</td>
</tr>
<tr>
<td>Diuretics</td>
<td>97</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>39</td>
<td>39</td>
<td>30</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>53</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>16</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Nitrates</td>
<td>43</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>20</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>
Profiles of Heart Failure
(Including ACEI as tolerated, diuretics, digoxin)

<table>
<thead>
<tr>
<th></th>
<th>REMATCH</th>
<th>FIRST</th>
<th>PROMISE</th>
<th>COPERNICUS</th>
<th>SOLVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>17</td>
<td>19</td>
<td>21</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>NYHA</td>
<td>IV</td>
<td>IV</td>
<td>III-IV</td>
<td>III B-IV</td>
<td>II-III</td>
</tr>
<tr>
<td>SBP</td>
<td>103</td>
<td>105</td>
<td>115</td>
<td>123</td>
<td>120</td>
</tr>
<tr>
<td>Na</td>
<td>135</td>
<td>137</td>
<td>139</td>
<td>137</td>
<td>140</td>
</tr>
<tr>
<td>6 mo mortality</td>
<td>45%</td>
<td>37%</td>
<td>28%</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>1 year mortality</td>
<td>76%</td>
<td>49%</td>
<td>40%</td>
<td>18.5%</td>
<td>16%</td>
</tr>
</tbody>
</table>
“Every attempt should be made to discontinue IV inotropic agents prior to discharge from the hospital. This will often require careful titration of vasodilating regimens and volume status as the inotropic therapy is weaned. Some patients will have symptomatic hypotension on an ACEI dose that was tolerated during dobutamine infusion and should not be considered to have failed weaning until lower ACEI dose, and if necessary, substitution of another vasodilator regimen has been attempted. …” June 1999
Summary of Patient Population

- REMATCH patients are a sicker patient population
- Patients assigned to medical management arm were optimized
REMATCH TRIAL CLINICAL RESULTS

Eric Rose, MD
REMATCH Principal Investigator
Chairman, Department of Surgery
Columbia University
New York, NY
Patient Enrollment

968 Patients Screened

128 Patients Randomized

LVAD Arm (n=67)

OMM Arm (n=61)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>LVAD (N=67)</th>
<th>OMM (N=61)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±9.1</td>
<td>68±8.2</td>
<td>0.22</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>17±5.3</td>
<td>17±4.5</td>
<td>0.86</td>
</tr>
<tr>
<td>Cardiac Index (l/min/sq.m)</td>
<td>1.9±0.5</td>
<td>2.0±0.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>1.8±0.7</td>
<td>1.8±0.7</td>
<td>0.48</td>
</tr>
<tr>
<td>IV Inotropes (%)</td>
<td>64</td>
<td>75</td>
<td>0.18</td>
</tr>
<tr>
<td>MLHF (Total score)</td>
<td>76±17</td>
<td>75±17</td>
<td>0.76</td>
</tr>
</tbody>
</table>
Kaplan-Meier plot illustrating the probability of survival of LVAS versus OMM patients after 92 deaths. Logrank analysis: $P=0.003$
Effectiveness Results

- 1 year survival doubled
- Absolute reduction of mortality rate of 27% at 1 year
- 2 year survival tripled
- Median Survival Time 408 days for LVAS patients vs 150 days for OMM
Effectiveness Conclusion

All-cause mortality reduced by 46% in LVAD patients

Primary Objective of 33% Exceeded
Serious Adverse Events / 30 Pt days

Days from enrollment:

- 0 - 30 days
- 31 - 90 days
- 91 - 180 days
- 181 - 360 days
- > 360 days

Bar chart showing the distribution of days from enrollment for different time periods, with bars indicating the number of serious adverse events for LVAD and OMM.
Serious Neurologic Events / 30 Pt days

Days from enrollment

- 0 - 30 days
- 31 - 90 days
- 91 - 180 days
- 181 - 360 days
- > 360 days

LVAD
OMM
Neurological Events in the LVAD Arm

LVAD Patients = 67
Neurological Events = 40

Stroke Subtype: N = 10
Ischemic = 6
Hemorrhage (SAH/ICH) = 2
Air emboli = 2
Bleeding & Infection Events

**Bleeding:**
- Majority of bleeds (67%) associated with LVAD implant or reimplant
- Similar to bridge experience

**Infection:**
- Specific complication of VAD use
- Initially unappreciated association with malnutrition
- Infection Guidelines developed
Median time spent in and out of hospital

Days spent in hospital: Median LVAD > Median OMM

Days out of hospital: Median LVAD > Median OMM

Days index hospital: Median LVAD > Median OMM
Quality of Life Assessment

• Hypothesis: QoL with LVAD should equal or exceed OMM group

• Instruments used:
  - SF-36 Health Survey (general health measure, 2 prespecified domains)
  - Minnesota Living with Heart Failure (disease specific QoL)
  - NYHA (functional status)
  - Beck Depression Inventory
  - EuroQOL (patient preferences)

• No QoL values imputed for dead patients
SF-36 Role/ Emotional

Months Post Enrollment

LVAD
OMM
SF-36 Physical Functioning

Months Post Enrollment

<table>
<thead>
<tr>
<th></th>
<th>LVAD</th>
<th>OMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>20</td>
</tr>
</tbody>
</table>
Minnesota Living with Heart Failure Total Score

Lower score equals less effect of HF on daily activities
VE LVAS Improves NYHA Functional Class

% NYHA Class III or Class IV

Month Post Enrollment

LVAD
OMM
Beck Depression Inventory

Clinical depression, 17
Summary of QoL Findings

- LVAD scores never worse than OMM (except short-term post-operative pain)
- LVAD generic QoL better than OMM at 12 months (key, pre-specified SF-36 domains)
- LVAD disease-specific QoL (MLHF) improved over OMM at 12 months but not significant statistically
- LVAD functional status (NYHA) significantly better than OMM
- LVAD reduced depressive symptoms to normal range (not seen in OMM)
QoL in Context

- LVAD physical function scores not normal, but analogous to patients receiving long-term hemodialysis and ambulatory heart failure patients.
- LVAD emotional-role scores better than those reported for clinical depression and similar to those for ambulatory heart failure patients.
Kaplan-Meier plot illustrating the probability of survival of LVAS versus OMM patients Feb 2002. Logrank analysis: P=0.001
Key Objective Conclusions

**Efficacy**

- Exceeded primary objective of trial by demonstrating that VE LVAS reduces all cause mortality in end-stage heart failure patients who are not candidates for cardiac transplantation
- Demonstrated statistical significance at 1 and 2 years.

**Safety**

- Incidence of AEs associated with implantation is higher than OMM patients
- Incidence of overall adverse events acceptable when compared to natural history of terminal illness
- Multiple opportunities for improvement identified
## What is Meaningful Benefit?

<table>
<thead>
<tr>
<th>Study (therapy)</th>
<th>1 year Mortality (% ) Control vs Tx</th>
<th>1 yr Relative Benefit (%)</th>
<th>Absolute Benefit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD (ACE Inhibitor)</td>
<td>14 vs 11</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>CONSENSUS (ACE Inhibitor)</td>
<td>62 vs 45</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>ATLAS (ACEI dosing)</td>
<td>14 vs 13.3</td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>COPERNICUS (Beta Blocker)</td>
<td>18.5 vs 11</td>
<td>41</td>
<td>7.5</td>
</tr>
<tr>
<td>RALES (Spironolactone)</td>
<td>25 vs 17</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>REMATCH (LVAD)</td>
<td>76 vs 49</td>
<td>36</td>
<td>27</td>
</tr>
</tbody>
</table>
SUMMARY AND CLOSING REMARKS

Donald A. Middlebrook
Vice President, Regulatory Affairs and Quality Assurance
Thoratec Corporation
Conclusions

Study scientifically validates safety and effectiveness:

- Strong evidence for clinically meaningful survival benefit
- VE LVAS is a well characterized, proven technology
- Reasonable evidence for safety particularly in context of terminal illness
- All QOL instruments showed sustained improvement trends over OMM
- Device provided unprecedented reduction in mortality in ESHF patients when compared to landmark drug studies
- VE LVAS is the only now proven alternative therapy for non-transplantable ESHF patients
The HeartMate VE LVAS should be approved for end stage heart failure patients ineligible for cardiac transplantation.